Amendments to the Claims

Claim 1 (currently amended): A method of performing a combined Chromatography and Mass Spectrometry analysis (C/MS) on at least one sample for the characterization of biomolecules species in the sample, which method comprises the steps of:

-*performing* an C/MS analysis(300);

-*generating* at least one first elution profile (305), ~~which~~ said first elution profile ~~is~~ being a multidimensional representation of the data resulting from the C/MS analysis wherein one dimension is an elution time of the chromatography, and one dimension is mass to charge ratio (m/z), and at least one dimension is a signal intensity, and in which of the elution profile a characteristic any variation in the signal intensity is an indication of the existence of a specific biomolecule species, and wherein the signal from each biomolecule species is dispersed forming a plurality of signal peaks associated with each biomolecule species in the elution profile; and

-*reassembling* the dispersed signal originating from one biomolecule species in the elution profile (310);

and ~~which method is **characterized in** that~~ further wherein said reassembling step ~~comprises~~ includes an automated annotation adapted to reassemble signal variations in the elution profile that originate from the same biomolecule species and generating a biomolecule map, said automated annotating being simultaneously based on at least both the elution time-dimension and the m/z-dimension.

Claim 2 (currently amended): The C/MS analysis method ~~according to~~ of claim 1, **wherein** the dispersion of signal from each biomolecule species arises from ~~the~~

~~existence of~~ different isotopes and/or charge states of the biomolecule species, and wherein the automated ~~annotation species~~ <u>annotating</u> reassembles the signal dispersion for essentially each biomolecule caused by ~~both~~ the different isotopes and/or different charge states of the biomolecule species.

Claim 3 (currently amended): The C/MS analysis method ~~according to~~ <u>of</u> claim 2, **wherein** the sample that comprises biomolecules species ~~has received~~ <u>includes</u> different chemical labels, ~~giving~~ <u>resulting in,</u> at least, a first chemically labelled biomolecule with a first label and a second mass-labelled biomolecule with a second label, ~~the chemical difference~~ <u>said labels</u> causing a further dispersion of the signal in the elution profile, and wherein the automated annotation reassembles the signal dispersion ~~inflicted~~ <u>caused</u> by the chemical labelling.

Claim 4 (currently amended): The C/MS analysis method ~~according to~~ <u>of</u> claim 3, **wherein** the chemical labels are mass labels ~~giving~~ <u>resulting in</u> at least a first mass labelled biomolecule with a first mass <u>label</u> and a second mass labelled biomolecule with a second mass <u>label</u>, <u>and wherein</u> the mass difference causes a dispersion of the signal in the elution profiles, and wherein the automated annotation reassembles the signal dispersion inflicted by the mass labelling.

Claim 5 (currently amended): The C/MS analysis method ~~according to~~ <u>of</u> claim 3, **wherein** the chemical labels are isotope labels ~~giving~~ <u>resulting in</u> at least a first isotope labelled biomolecule ~~comprising~~ <u>including</u> isotopes of a first type and a second isotope labelled biomolecule ~~comprising~~ <u>including</u> isotopes of a second type, the different isotopes causing a dispersion of the signal in the elution profiles, and

wherein the automated annotation reassembles the signal dispersion inflicted by the isotope labelling.

Claim 6 (currently amended): The C/MS analysis method of claim 2 ~~according to any of claims 2 to 5~~, **wherein** the automated annotation in the reassembling of dispersed signals uses knowledge of the mass spectrometer resolution.

Claim 7 (currently amended): The C/MS analysis method ~~according to~~ of claim 6, **wherein** the automated annotation in the reassembling of dispersed signals uses a priori assumptions on the relations between different charge states and/or different isotopes of the same biomolecule species in the reassembling of dispersed signals.

Claim 8 (currently amended): The C/MS analysis method ~~according to~~ of claim 6, **wherein** the automated annotation in the reassembling of dispersed signals uses ~~the~~ an assumption that a first signal pattern associated with a first charge state of a biomolecule species has an resemblance with a second signal pattern associated with a second charge state of the biomolecule species.

Claim 9 (currently amended): The C/MS analysis method ~~according to~~ of claim 6, **wherein** the automated annotation in the reassembling of dispersed signals uses ~~the~~ an assumption that a first isotope distribution associated with a first charge state of a biomolecule species has an resemblance with a second isotope distribution associated with a second charge state of the biomolecule species.

Claim 10 (currently amended): The C/MS analysis method of claim 6 ~~according to any of claims 6 to 9~~, **wherein** the automated annotating comprises the steps of:

–a) *finding and marking* peaks in the signal variation of the first elution profile(310:1);

- b) *defining* a first set of spots, wherein each spot ~~comprising~~ including at least one primary feature and said spots ~~having~~ have a variable extension in the m/z-dimension and a variable extension in the elution time dimension, and each spot is assumed to correspond at least to a specific charge state and an isotope or group of isotopes of a biomolecule (310:2);

- c) *constructing* a peptide map entry for each spot by detecting a set of regions with a known structural relationship and confining the patterns from one peptide species within the elution profile (310:3); and

-d) *repeating* ~~step~~ steps (b) to (d) for each spot, and wherein,

in the step of constructing a peptide map entry is created if for the charge state the structural relationships of the set of regions are essentially consistent and significant, and if no charge state giving essentially ~~the~~ known the structural relationships of the set of regions can be found, an incomplete peptide map entry is created from the spot itself.

Claim 11 (currently amended): The C/MS analysis method ~~according to~~ of claim 10, **wherein~~,~~** the step of constructing a peptide entry comprises ~~that~~, for each putative charge z~~, if possible~~, detecting additional isotopes at $m/z \pm 1/z$, $m/z \pm 2/z$, etc. (310:3:1).

Claim 12 (currently amended): The C/MS analysis method ~~according to~~ of claim 10, **wherein**~~,~~ the step of constructing a peptide entry comprises ~~that~~, for each putative charge *z*~~, if possible~~, detecting additional charge states at $(m\text{-}1)/(z\pm1)+1$, $(m\text{-}1)/(z\pm2)+1$, etc. (310:3:2).

Claim 13 (currently amended): The C/MS analysis method ~~according to~~ of claim 10, **wherein**~~,~~ the step of constructing a peptide entry comprises ~~that~~, for each putative charge *z*~~, if possible~~, detecting different label variants, wherein the expected displacement is specific for the labelling scheme used (310:3:3).

Claim 14 (currently amended): The C/MS analysis method ~~according to~~ of claim 10, **wherein** the step of constructing a peptide entry of the automated annotating comprises at least two different modes reflecting the resolution characteristics of the mass spectrometer.

Claim 15 (currently amended): The C/MS analysis method ~~according to~~ of claim 14, **wherein** the resolution of the spectrometer is dependent on m/z and described by a spectrometer resolution parameter (R(m/z)), and the charge state assignment step ~~comprises~~ includes a high resolution mode and a low resolution mode, wherein the shifting between the modes is dynamical, and the criteria for shifting between the modes is dependent on m/z, z and the spectrometer resolution parameter.

Claim 16 (currently amended): The C/MS analysis method ~~according to~~ of claim 15, **wherein** for given m/z and z values the high resolution mode is used if:

$$\frac{m}{z} < \frac{1}{z} R\beta$$

wherein R spectrometer resolution parameter and β is an empirically predefined parameter, and

the low resolution mode is used otherwise.

Claim 17 (currently amended): The C/MS analysis method ~~according to~~ of claim 1, **wherein** the method further comprises the steps of:

-*matching* individual biomolecule maps (315) generated in the reassembling step (310), to form a global annotation;

-*performing measurement and evaluation* (320) for profiling ~~the~~ a relative abundance of some of the individual biomolecule species across different samples, wherein the abundance profiles are based on the global annotation obtained in the preceding steps.

Claim 18 (currently amended): The C/MS analysis method ~~according to~~ of claim 17, **wherein** the method further comprises a step of defining subsets of biomolecule species (325), said step of defining subsets adapted for selecting subsets for further analysis, and the selection being based on variations in ~~the~~ a relative abundance of some biomolecule species across different samples.

Claim 19 (currently amended): A measurement system for performing a combined Chromatography and Mass Spectrometry analysis (C/MS) on at least one sample for characterization of biomolecules species in the sample, wherein the measurement system comprises at least one chromatography column (125), a mass spectrometer interface (130), a mass spectrometer (135) and means for control and analysis (140,145), and the measurement system is adapted to:

-*perform* an C/MS analysis;

-*generate* at least one first elution profile, ~~which~~ said first elution profile ~~is~~ being a multidimensional representations of the data resulting from the C/MS analysis wherein one dimension is an elution time of the chromatography, and one dimension is mass to charge ratio (m/z), and at least one dimension a signal intensity, and in which of the elution profile a characteristic any variation in the signal intensity is an indication of the existence of a specific biomolecule species, and wherein the signal from each biomolecule species is dispersed forming a plurality of signal peaks associated with each biomolecule species in the elution profile; and

-*reassemble* the dispersed signal originating from one biomolecule species in the elution profile,

and ~~which~~ further wherein said measurement system is ~~**characterized in**~~ that reassembling ~~comprises~~ methodology includes an automated annotation adapted to reassemble signal variations in the elution profile that originate from the same biomolecule species and generating a biomolecule map, said automated annotating being simultaneously based on at least both the elution time-dimension and the m/z-dimension.

Claim 20 (currently amended): The measurement system ~~according to~~ of claim 19, further adapted to, in the automated annotation of dispersed signals, use knowledge of the mass spectrometer resolution for reassembling of signals originating from the same biomolecule species.

Claim 21 (currently amended): The measurement system ~~according to~~ of claim 20, **wherein** the automated annotating may operate in at least two different modes reflecting the resolution characteristics of the mass spectrometer.

Claim 22 (currently amended): The measurement system ~~according to~~ of claim 21, **wherein** ~~the~~ resolution of the spectrometer is dependent on m/z and described by a spectrometer resolution parameter (R(m/z)), and the charge state assignment step ~~comprises~~ includes a high resolution mode and a low resolution mode, wherein the shifting between the modes is dynamical, and the criteria for shifting between the modes is dependent on m/z, z and the spectrometer resolution parameter.

Claim 23 (currently amended): Computer program products directly loadable into the internal memory of a processing means within the means for controlling an analysing (140,145), comprising the software code means adapted for controlling the steps of claim 1 ~~any of the claims 1 to 18~~.

Claim 24 (currently amended): Computer program products stored on a computer usable medium, comprising readable program adapted for causing a processing means in a processing unit within the means for controlling an analysing (140,145), to control an execution of the steps of claim 1 ~~any of the claims 1 to 18~~.